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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/512,701 | 02/25/2000 | JOHN P. LEONARD | GI5229FWC-DIV1 | 7087 |

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| EXAMINER | |
|---|---|
| MINNIFIELD, NITA M | |
| ART UNIT | PAPER NUMBER |
| 1645 | |

DATE MAILED: 01/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/512,701 | LEONARD ET AL. | |
| | Examiner | Art Unit | |
| | N. M. Minnifield | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *10; 12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Response to Amendment*

1. Applicants' after final filed November 28, 2001 is acknowledged and has been entered. Claims 16-20 are now pending in the present application. All rejections have been withdrawn in view of Applicants' arguments set forth in the after final. However, it is noted that the following new grounds of rejection have been set forth and therefore the following Office Action is NON-FINAL.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feldman et al (1992) taken with Trinchieri et al (1992).

The claimed invention is directed to a method of treating rheumatoid arthritis in a human subject, said method comprising administering IL-12 antagonist (0.05-25 mg/kg in a pharmaceutically acceptable carrier) that binds IL-12; wherein said antagonist is an antibody immunoreactive with IL-12 or an antibody fragment immunoreactive with IL-12.

Feldman et al teach that by "... using neutralizing antisera TNF-alpha and TNF-beta (potent inducers of IL-1) it was found that neutralizing TNF-alpha virtually abrogated IL-1 production from these cultures. This study was surprising, as many signals in the RA joint could also induce IL-1 (e.g. IL-1 itself, GM-CSF, IFN-gamma, immune complexes). However, it was reproducible, and led to our initial awareness of the importance of TNF-alpha in the pathogenesis of RA, and

led to further experiments to investigate the role of TNF-alpha in RA. TNF-alpha was also detected by immunostaining both in the membrane and in the cartilage pannus junction." (p. 250). Feldman et al teach that the *in vitro* data suggested that TNF-alpha is important in the rheumatoid process and that experiments were performed to test the concept that TNF-alpha was a useful target for therapy. "Experiments were performed in the murine collagen induced arthritis model (CIA), which has many similarities to human RA. A hamster anti murine TNF-alpha antibody was capable of significantly ameliorating CIA, if injected before or during the arthritis process..." (p. 253). Feldman et al teaches that this improvement *in vivo* helped provide the rationale for evaluating the effect of blocking TNF-alpha in patients with rheumatoid arthritis. The use of a chimeric anti TNF-alpha antibody showed that the acute phase response was diminished and a good clinical response, as judged by pain, swelling of joints, morning stiffness or joint tenderness was observed (p. 253). Feldman et al also sets forth that "[O]f the many cytokines expressed in the rheumatoid joint TNF-alpha was identified as being of likely pathogenic based on many aspects, summarized in Fig. 4. This has led to a demonstration that blocking TNF-alpha is beneficial in animal models of arthritis, and most importantly to a clinical trial which has substantiated the concept that TNF-alpha is an important target for therapy in RA. The clinical benefit of blocking TNF demonstrated with a chimeric antibody in RA suggests that other ways of blocking TNF action should also be of benefit. That there is benefit in blocking TNF-alpha does not exclude the possibility that blocking other cytokines may also yield considerable clinical benefits." (p. 254). The prior art teaches the

method of treatment of rheumatoid arthritis, but not the specific administration of IL-12 antagonist (anti-IL-12).

However, Trinchieri et al teaches that IL-12 (NSKF) *in vivo* is likely to play an important physiological role in the regulation of immune responses and inflammation and that this cytokine offers promising possibilities for therapeutical use (p. 356). Figure 1 depicts some of the known function of IL-12. Trinchieri et al teaches that IL-12 induces TNF-alpha and other lymphokines (p. 359). Since the art teaches the concept that a block in the production of TNF-alpha production would be a means/therapy for the treatment of RA and that IL-12 induces TNF-alpha, it would have been obvious to a person of ordinary skill in the art at the time of the invention to use the teachings of the prior art as set forth above with the expected benefit of developing a method of using an IL-12 antagonist (anti-IL-12), to block IL-12 which in turn to decreases the production of TNF-alpha to treat RA in humans. Both Feldman et al and Trinchieri et al teach the use of antibodies in the treatment of RA. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a composition that would block or hinder TNF-alpha production since the art teaches that TNF-alpha is involved in RA. Blocking the production of TNF-alpha by using an IL-12 antagonist, which would inhibit its production would give a reasonable expectation of success. With regard to the specific dose of IL-12 antagonist, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine the optimum or therapeutically effective amount of IL-12 antagonist (antibody to IL-12), since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. *In*

*re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). The claimed invention is prima facie obvious in view of the prior art absent any convincing evidence to the contrary.

7. No claims are allowed.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

9. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record in the present application.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nita M. Minnifield whose telephone number is 703-305-3394. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Rita M. Wakefield
Primary Examiner
Art Unit 1645
January 18, 2002